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A systematic review on concurrent aneuploidy screening and preimplantation genetic testing for hereditary disorders: what is the prevalence of aneuploidy and is there a clinical effect from aneuploidy screening?

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ABSTRACT:

Introduction: In assisted reproductive technology, aneuploidy is considered a primary cause of failed embryo implantation. This has led to the implementation of preimplantation genetic testing for aneuploidy in some clinics. The prevalence of aneuploidy and the use of aneuploidy screening during preimplantation genetic testing for inherited disorders has not previously been reviewed. Here, we systematically review the literature to investigate the prevalence of aneuploidy in blastocysts derived from patients carrying or affected by an inherited disorder, and whether screening for aneuploidy improves clinical outcomes. **Material and methods:** PubMed and Embase were searched for articles describing preimplantation genetic testing for monogenic disorders and/or structural rearrangements in combination with preimplantation genetic testing for aneuploidy. Original articles reporting aneuploidy rates at the blastocyst stage and/or clinical outcomes (Positive human chorionic gonadotropin, gestational sacs/implantation rate, fetal heartbeat/clinical pregnancy, ongoing pregnancy, miscarriage, or live birth/delivery rate on a per transfer basis) were included. Case studies were excluded. **Results:** Of the 26 identified studies, none were randomized controlled trials, three were historical cohort studies with a reference group

not receiving aneuploidy screening, and the remaining were case series. In weighted analysis, 34.1 % of 7749 blastocysts were aneuploid. Screening for aneuploidy reduced the proportion of embryos suitable for transfer, thereby increasing the risk of experiencing a cycle without transferable embryos. In pooled analysis the percentage of embryos suitable for transfer was reduced from 57.5 to 37.2 % following screening for aneuploidy. Among cohort studies, one reported significantly improved pregnancy and birth rates but did not control for confounding, one did not report any statistically significant difference between groups, and one properly designed study concluded that preimplantation genetic testing for aneuploidy enhanced the chance of achieving a pregnancy while simultaneously reducing the chance of miscarriage following single embryo transfer. **Conclusion:** On average aneuploidy is detected in 34 % of embryos when performing a single blastocyst biopsy derived from patients carrying or affected by an inherited disorder. Accordingly, when screening for aneuploidy, the risk of experiencing a cycle with no transferable embryos increases. Current available data on the clinical effect of preimplantation genetic testing for aneuploidy performed concurrently with preimplantation genetic testing for inherited disorders is sparse, rendering the clinical effect from preimplantation genetic testing for aneuploidy difficult to access.

Keywords

Preimplantation genetic testing, Clinical outcomes, Aneuploidy screening, Comprehensive chromosome screening, Systematic review, preimplantation genetic diagnosis; preimplantation screening

Abbreviations:

aCGH	array comparative genomic hybridization
ART	assisted reproductive technology
ESHRE	European Society for Human Reproduction and Embryology
FISH	fluorescence in situ hybridization
MFA	mean female age

PGT preimplantation genetic testing

PGT-A PGT for aneuploidy

PGT-M PGT for monogenic disorders

PGT-SR PGT for structural rearrangements

PRISMA Preferred reporting items for systematic reviews and meta-analyses

Key message:

One third of embryos derived from patients carrying or affected by an inherited disorder are aneuploid. Hence, prioritizing embryos by ploidy status should in theory improve clinical success rates per transfer. The design and quality of the current available data does not allow a conclusion.

INTRODUCTION

Preimplantation genetic testing (PGT) is defined as genetic testing of biopsied material from in vitro fertilized pre-implantation embryos from couples carrying or affected by a hereditary disorder with the aim of identifying unaffected embryos for transfer. The first case of PGT for an inherited disorder was reported by Handyside et al. in 1989 on a couple at risk of transmitting an X-linked recessive disease.[1] Gender selection was performed on biopsied material from cleavage stage embryos by Sanger sequencing followed by transfer of female embryos. Shortly thereafter, Sanger sequencing was adapted for direct analysis of monogenic mutations,[2] and increased diagnostic accuracy was obtained by simultaneous analysis of short tandem repeats.[3] Technological developments led to the introduction of fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), single nucleotide polymorphism arrays, karyomapping and next generation sequencing, making PGT possible not only for monogenetic disorders but also for chromosomal insertions, duplications, deletions and translocations. PGT performed for monogenic diseases and chromosomal structural rearrangements are referred to as PGT-M and PGT-SR, respectively.[4] Based on data collected from transfer of 6277 embryos in 4025 PGT cycles by the European Society of Human Reproduction and Embryology (ESHRE) PGT consortium, PGT for inherited diseases is currently performed with clinical implantation rates (fetal heartbeat/embryo transferred), clinical pregnancy rates (positive heartbeat/embryo transfer) and delivery rates (delivery/embryo transfer) of 23, 31 and 25 %, respectively.[5]

The current gold standard for prioritization of embryos for transfer during assisted reproductive technology (ART) is based upon morphological and developmental assessment of individual embryos sometimes aided by time-lapse imaging,[6] which is biased by its inherently subjective scoring systems.[7] It has been acknowledged that aneuploidy is common in human preimplantation embryos, affecting approximately 25 % of embryos derived from young women, and increases with female age in women receiving ART.[8] Furthermore, aneuploidy is prevalent in products of conception from miscarriages.[9] Altogether, these facts indicate that selection against aneuploidy could benefit clinical outcomes. Although some degree of correlation between the morphology grade and the ploidy state of the embryo exists,[10–13] aneuploidy cannot reliably be predicted based

on embryo morphology alone.[14,15] Preimplantation genetic testing for aneuploidy (PGT-A) is numerical chromosomal analysis of biopsied cells from embryos with the purpose of transferring euploid embryos and has previously been used in ART in order to optimize clinical outcomes on indications such as advanced maternal age, repeated implantation failure, recurrent miscarriages and severe male factor infertility. PGT-A was initially performed by FISH (PGT-A version 1.0), which allowed the enumeration of a limited number of chromosomes (originally limited to chromosome Y, X, 13, 18 and 21), on biopsies from cleavage stage embryos.[16] Despite the expectations that cleavage stage biopsy and FISH would enhance clinical outcomes, numerous randomized controlled trials failed to show any improvements of live birth rates and even showed decreased live birth rates in women of advanced maternal age.[17]

The lack of clinical effect of PGT-A version 1.0 was attributed to a variety of factors, such as the limited number of chromosomes examined by FISH, since aneuploidy may affect all chromosomes.[18,19] Further, cleavage stage embryos are more prone to mosaicism and aneuploidy than blastocysts,[14,20,21] and hence does not accurately predict the chromosomal profile of the resulting blastocyst.[22,23] Finally, a negative impact on embryo implantation potential seems to be caused by biopsy at the cleavage stage compared with biopsy at the blastocyst stage.[24,25] Hence, FISH and cleavage stage biopsy are now rarely used as tools for PGT-A, with laboratories switching to biopsy at the blastocyst stage and to techniques that allow screening of the entire chromosome set, such as aCGH, single nucleotide polymorphism array (later also commercialized as karyomapping), and next generation sequencing, also referred to as PGT-A version 2.0 and comprehensive chromosome screening. Importantly, although the mentioned techniques allow screening of the entire chromosome set, they all have their own limitation. One of the more common problems is the detection of sequence-identical chromosomal duplications, such as mitotic trisomies or uniparental disomy.

The combination of comprehensive chromosome screening and blastocyst biopsy was by some expected to be able to succeed where PGT-A version 1.0 failed. Initially, a systematic review and a meta-analysis independently concluded that comprehensive chromosome screening enhanced clinical outcomes in patients with normal ovarian reserve.[26,27] However, others claimed that the small size of the limited number of RCTs currently published, did not justify the use of comprehensive chromosome screening in clinical practice. [28] A recent multicenter study comparing clinical outcomes following next generation sequencing-based PGT-A and

morphological analysis showed an effect of PGT-A in older patients (35-40 years) only.[29] Thus, a recent consensus report from the American Society of Reproductive Medicine stated that *"At present, however, there is insufficient evidence to recommend the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients"*.[30] Recently, and published after the publication of the statement by the American Society of Reproductive Medicine, a large historical cohort study reported a statistically significant improvement on live births/cycle following PGT-A in women ≤ 40 years compared to a group not receiving PGT-A. Furthermore, implantation and live birth rates were unchanged across female age following PGT-A.[31] From a purely biological perspective, selecting euploid embryos should increase clinical success rates on a per transfer basis, but factors such as quality of embryo culture and biopsy technique, as well as diagnostic methods applied, may explain the somewhat divergent findings currently reported in the literature.

The application of PGT-A in patients referred to PGT for inherited disorders has not been systematically reviewed. Hence, we looked at the available literature reporting on concurrent PGT-A and PGT-M/SR with the aim of investigating the prevalence of aneuploidy and clinical effect of aneuploidy screening. Since blastocyst stage biopsy has been shown to be superior to cleavage stage biopsy with respect to analytic precision and clinical outcomes,[14,20–25] only studies performing biopsy on blastocysts were considered relevant for this review.

MATERIAL AND METHODS

This review was performed and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including the PRISMA flowchart and checklist.

In- and exclusion criteria

Inclusion criteria were 1) that PGT-SR or PGT-M was performed in combination with PGT-A and 2) that aneuploidy rates and/or clinical outcomes were reported. Clinical outcomes were defined as either positive human chorionic gonadotropin gestational sacs/implantation rate, fetal

heartbeat/clinical pregnancy, ongoing pregnancy, miscarriage/spontaneous abortion, ongoing pregnancy or live birth/delivery rate reported on a per transfer basis.

Exclusion criteria were 1) Case-studies, 2) Studies not performing trophectoderm biopsy or where aneuploidy or clinical outcomes specific for trophectoderm biopsies could not be extracted, 3) Reviews, 4) Redundant publications (Same data used for two publications) and 5) Studies lacking important meta data relevant for interpreting and/or understanding the data.

Literature search

Searches were performed in PubMed and Embase to identify publications regarding concurrent PGT-A and PGT-M/SR. This was done using separate comprehensive search strategies for PubMed and Embase. The search strings can be seen in Supporting Information Appendix S1. Abstracts were screened by C.L.F. Toft and full text reviewed by I.S. Pedersen and C.L.F. Toft, who also agreed on the final selection of papers.

Data extraction pooling

Data was extracted directly from the articles and/or supplementary material when needed. P-values were reported here as reported by the authors in the original article. In case p-values were not reported, they were calculated where needed. In cases where data or statistical calculations seemed to have been misreported, the corresponding author was contacted for clarification. Authors were not contacted to obtain meta data. Data was pooled and weighted regarding the number of embryos analyzed to obtain a weighted average aneuploidy rate and weighted average proportions of suitable embryos prior to and post PGT-A. Even though measured aneuploidy rates are in theory affected by the platform used for PGT-A, the potential differences caused by different platforms were considered neglectable. Hence, weighted aneuploidy rates were performed across studies utilizing different PGT-A platforms. Since the aim was to report on aneuploidy in PGT in general, differences in mean female age (MFA) was not considered an issue when calculating the weighted aneuploidy rate. Data pooling with respect to clinical outcomes was not possible due to the heterogeneity of the studies.

Tools for assessment of risk of bias are mainly developed for randomized controlled trials, cohort and case-control studies. Since the vast majority of studies included in this review were case series with no reference group, no formal assessment of risk of bias was performed, as the risk would in any case be considerable.

Statistical analyses

All statistical analyses were performed using R version 1.1.453 (https://support.rstudio.com/). Testing for the null hypothesis that proportions (both aneuploidy and clinical outcomes) in two groups were the same were performed using chi-squared test or Fisher's exact test. P-values less than 0.05 were considered statistically significant.

RESULTS

Literature search and study characteristics

A total of 1717 publications were identified through Medline (840) and PubMed (877). Screening for duplicates resulted in 1291 unique publications. Title and abstract screening resulted in 73 papers. Full text screening resulted in 26 publications fulfilling the inclusion criteria [18,32,41–50,33,51–56,34–40]. Interestingly, no randomized controlled trials were identified. Three historical cohort studies with a reference group not receiving aneuploidy screening were identified, while the remaining studies were case series without a reference group. The search was last updated on the first of July 2019. A flow diagram of the screening process in shown in Figure 1. Table 1 summarizes the main characteristics of the 26 studies included in this review in chronological order of publication date.

The included studies were published between 2011 and 2019. The number of patients receiving trophectoderm biopsy was not available in 4 studies. MFA of patients receiving trophectoderm biopsy was available in 15 studies and ranged from 29.2 to 38.1 years. The number of embryos successfully analyzed for both aneuploidy and genetic disorder ranged from 12 to 1498. No studies reported performing sequential biopsies or rebiopsy. All included studies reported aneuploidy rates. 17 studies reported clinical outcomes with three retrospective studies included a reference group. CGH, aCGH, next generation sequencing, single nucleotide polymorphism

array/karyomapping and quantitative PCR were used for aneuploidy detection (Table 1). Diagnosis of x-linked disorders was classified as PGT-M in all of the included studies.

Prevalence of aneuploidy in patients carrying or affected by a genetic disorder

The reported aneuploidy rates are listed in Table 1 and illustrated in Figure 2. The aneuploidy rate ranged from 17.2 to 83.3 %. The weighted average aneuploidy rate of the 7749 embryos was 34.1 % (95 % CI; 33.1 % to 35.2 %) (Figure 2, top bar). For PGT-M, aneuploidy ranged from 19.0 to 83.3 % with a weighted average of 35.9 %. For PGT-SR, aneuploidy ranged from 17.2 to 53.3 % with a weighted average of 32.5 %. Comparing PGT-M and PGT-SR there was a small but statistically significant difference between the two groups with aneuploidy being more prevalent in the PGT-M group ($P = 0.002$).

The effect of PGT-A on the number of transferable embryos

The percentage of embryos suitable for transfer prior to and post PGT-A are shown in Figure 3A. Combining the data, the weighted average number of embryos being suitable for transfer prior to and post PGT-A dropped from 57.5 to 37.2 % (95 % CI; prior: 56.3 % to 58.6 %, post: 36.1 % to 38.4 %) (Figure 3A, top bar). 17 of 22 studies reported a statistically significant difference in the number of suitable blastocysts for transfer prior to and post PGT-A (Figure 3A). Comparing PGT-M and PGT-SR, there were no statistically significant difference between the percentage of blastocysts suitable for transfer prior to and post PGT-A ($P = 0.8$ and $P = 0.6$, respectively, Figure 3B).

The effect of PGT-A on the percentage of cycles with no transfer

Screening for aneuploidy significantly increased the percentage of non-transferable embryos. In one study, embryo transfer was performed in 81 % of cycles (1688/2084) while only 67 %of cycles had transferable embryos following screening for aneuploidy (212/317).[54] In another study, out of 304 cycles, 71 % of cycles had suitable embryos for transfer following PGT-M/SR, which was reduced to 60 % following aneuploidy screening.[36] Minasi *et al.* reported the percentage of cycles with no transferable embryos following aneuploidy screening to be similar in patients

affected by monogenic disorders and structural rearrangements. The remaining studies did not provide any data on the increase in frequency of cycles with no transfer following aneuploidy screening.

Clinical outcomes of concurrent PGT-A and PGT-M/SR

Of the reviewed literature, 17 publications reported on clinical outcomes following PGT-A (Table 1). Only three studies included a reference group not receiving PGT-A (Table 1, Figure 4).[34,50,54] The average number of embryos transferred in the PGT-A and reference group for the three historical cohort studies are shown in Figure 4D. Only Hou *et al.* performed single embryo transfer in both groups where the Goldman *et al*. and Rechitsky *et al.* transferred more embryos in the reference group compared with the PGT-A group. Of the three studies, one did not achieve statistically significant results (Figure 4B).[50] The other two studies reported significantly improved clinical outcomes compared to the reference group (Figure 4A and C).[34,54] The study by Hou *et al.* contained age-matched cohorts (MFA of 29.02 vs. 29.34, $P = 0.328$) while the study by Rechitsky *et al.* did not disclose the MFA of the reference group. Hence, it cannot be excluded that the reported clinical effect from PGT-A reported by Rechitsky et al. might be caused by comparison of non-age-matched cohorts. Furthermore, it should be noted that the study by Rechitsky *et al.* performed both cleavage and blastocyst stage biopsy and even though clinical outcomes following blastocyst biopsy could be deferred from the article in case of the PGT-A data, this was not possible for the reference group. Of the 196 embryo transfers, 158 and 38 were following blastocyst and cleavage stage biopsy, respectively. Contrary to previous reports in the literature,[14,20,22,23] the data from Rechitsky *et al.* showed no significant differences in clinical outcomes between the two biopsy stages for any of the three parameters reported ($P > 0.95$ for all three parameters).

Mosaicism

Of the 26 publications, six studies reported on the prevalence of mosaicism. One publication reported mosaicism on a per chromosome level only.[51] The remaining five publications reported on mosaicism ranging from 0 % (0/175 and 0/18 embryos) to 10.8 % (11/102 embryos) with the two largest studies reporting 3.7 (42/1122 embryos) and 6.8 % (44/646).[34,36,39,43,46] Three of the six

studies details their classification and transfer policy with respect to mosaic embryos, [34,39,51] with two never transferring mosaic embryos,[34,39] and one considering mosaic embryos for transfer in the case that there was no euploid embryos available and that the level of mosaicism was 40 % or less. [51] The remaining three studies do not detail their classification of or transfer policy with respect to mosaic embryos. [36,43,46]

DISCUSSION

This review presents data from the 26 publications currently published about concurrent PGT-A and PGT-M/SR, which report on aneuploidy rates and/or clinical outcomes. Only three studies included a reference group. All three were historical cohort studies.

Despite the relatively young age of the patient cohort (ranging from 29.2 to 38.1), a significant proportion of embryos (34.1 %, 95 % CI; 33.1 % to 35.2 %) were aneuploid, indicating that a substantial fraction of embryos derived from couples seeking PGT for inherited disorders might be unsuitable for transfer. A wide range of aneuploidy frequencies were observed ranging from 17.2 to 83.3 %. Removing the bias introduced by analyzing a small number of embryos (by including studies of more than 100 embryos) resulted in an aneuploidy frequency from 21.5 to 56.5 %. This is still a wide range that cannot be explained simply by differences in MFA, but more likely by variations in the embryo handling procedures and diagnostic setups of individual clinics and laboratories. This underlines the need for further evaluation of the use of PGT-A.

Although aneuploidy was significantly more prevalent in PGT-M compared to PGT-SR (35.9 versus 32.5 %, $P = 0.002$) this finding is of little value since the data does not allow control for confounding variables, the most important being female age in the case of aneuploidy.

Aneuploidy is considered a significant contributor to implantation failures experienced during ART, but it is unknown if infertile couples are especially prone to create aneuploid embryos compared to fertile couples. Since most couples referred for PGT-M/SR are fertile, comparison of the ART and PGT cohort might help answer this question. Although the data presented here does not allow a strict age-matched comparison of prevalence of aneuploidy between the fertile (PGT-M/SR) and infertile patient (ART) cohorts, the weighted aneuploidy rate of 34.1 % in the PGT-M/SR cohort is comparable to that previously reported in a large ART study within the same age range, varying from about 22 to 49 %.[8]

PGT-A substantially increases the number of non-transferable embryos compared to PGT-M/SR alone (Figure 3A). All but four studies reported a statistically significant reduction in the percentage of embryos being suitable for transfer before and after PGT-A. The remaining four studies most likely failed to reach statistically significant differences due to the small sample size.[43,44,53,55] As a direct consequence of this, opting for PGT-A will most likely increase the risk of experiencing a cycle with no transferable embryos, and patients should therefore be informed about this risk during counseling on when to opt for PGT-A or not as well as about the on-going discussion of a clinical effect. This risk is expected to increase with both female age (as aneuploidy increases) and with decreasing ovarian reserve, meaning that risk counseling should consider these factors.

With respect to clinical outcomes, the currently published studies either lack an (age-matched) reference group, proper sample size and/or control of confounding variables such as the stage of biopsy, MFA and the number of embryos transferred per transfer, to allow a proper evaluation of the effect of PGT-A. We only identified three studies which had included a reference group of which two reported improved clinical outcomes,[34,54] while one failed to show an effect.[50] They were all historical cohort studies. One study performed both cleavage and blastocyst stage biopsy, of which the ratio with respect to the reference group was undisclosed,[54] complicating comparison as implantations rates are affected by the stage of embryo biopsy.[24,25] The study by Goldman *et al.* included only 32 and 8 patients in the PGT-A and reference group, respectively, making it difficult to detect small but significant differences. The last study indicated a benefit from PGT-A with respect to clinical outcomes.[34] Comparison to clinical outcomes reported in most recent report from the ESHRE PGT consortium would have been interesting but are not meaningful due to the degree of heterogeneity between the two datasets. In conclusion, randomized controlled trials of sufficient size are needed to draw final conclusions on a clinical effect of PGT-A.

The issue of PGT-A is presently intensely discussed. In that regard, it is important that any debate and evaluation of PGT-A with respect to clinical outcomes is based and performed on a per transfer basis. This is important, since the purpose of PGT-A is to aid in prioritization of embryos for transfer. Hence, PGT-A is unlikely to enhance cumulative live birth rates, as cumulative transfer will ultimately lead to transfer of the "best" embryo in a given embryo cohort. In worst case, PGT-A might even decrease cumulative live birth rates as misdiagnosis can lead to viable embryos being discarded. On the other hand, PGT-A might decrease miscarriage rates, and reduce

time to live birth. One of the main arguments against the use of PGT-A is the current limited knowledge on how to interpret the result of a trophectoderm biopsy due to embryonic mosaicism, the presence of one or more genetically distinct cells lines within the embryo, which is reported to affect 3-24 % of human blastocysts.[21] This may lead to false conclusions e.g. in case of isolated aneuploid groups of cells within the trophectoderm in an embryo with an euploid inner cell mass or vice versa. Only a few of the included publications report on mosaicism making it difficult to assess the impact. On top, information regarding how mosaic embryos are classified, and their corresponding transfer policy were rarely clear or provided. It should be kept in mind that aneuploidy rates will differ depending on whether mosaic embryos are classified as aneuploid or not, which is why this should always be detailed. The few rates of mosaicism reported in the included studies is in line with previous studies, showing that mosaic embryos constitute a small but potentially significant part of the embryo cohort, with potential to produce liveborn offspring.[57] In general, if aneuploidy screening is performed, and there is no euploid embryos available, mosaic embryos could be prioritized based on the chromosome(s) affected by aneuploidy, the type of aneuploidy and the degree of mosaicism detected,[57–60] preferably according to guidelines presented by the Preimplantation Genetic Diagnosis International Society (PGDIS) and Controversies in Preconception, Preimplantation and Prenatal Diagnosis (COGEN).[61,62] In general, each center utilizing PGT-A should develop evidence-based guidelines for embryo prioritization to ensure standardization of the treatment and transparency to both patients and piers. [63] Given the multitude of different factors influencing clinical outcomes following PGT-A, including the complex issue of mosaicism, even well documented guidelines need validation and may not be transferable from one center to another. Hence, comprehensive validation of PGT-A prior to clinical implementation seems necessary. Prospective, blinded, non-selection studies as performed and described by Scott *et al*. seems essential to evaluate the predictive value of PGT-A on a per center basis.[64] Such a study design allows direct measurement of the predictive value of ploidy calls with regard to their effect on clinical outcomes and hence provide the best possible data to guide the decisions on whether to apply PGT-A or not in PGT-M/SR in a given clinical setting. The predictive values might even be provided to patients when deciding whether to opt for PGT-A.

CONCLUSION

The current published literature reveals that aneuploidy affects one third of preimplantation human blastocysts, which upon transfer might lead to implantation failure, abortion or birth of affected children. Given these numbers, PGT-A concurrently with PGT-M/SR should in theory be able to enhance clinical outcomes on a per transfer basis, but the current available literature is sparse or of insufficient quality. Importantly, studies should seek to minimize impact from confounding variables such as the stage of biopsy and number of embryos transferred between the treatment and control group as well as seeking to compare age-matched cohorts. Although the available data may indicate an improvement in crude clinical outcome in accordance with expectations based on biological facts, routine use of PGT-A concurrently with PGT-M/SR with the aim of improving clinical outcomes are not supported by substantial evidence. Hence, randomized controlled trials are warranted and, preferably, should be accompanied by on site non-selection studies prior to implementation of PGT-A.

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Supporting information legend:

Appendix S1. PubMed and Embase search strings.

Table and figure legends:

Table 1: Overview of the articles fulfilling criteria for inclusion.

Figure 1: PRISMA flowchart describing the screening process. PGT-M, preimplantation genetic testing for monogenic disorders; PGT-SR, preimplantation genetic testing for structural rearrangements; PGT-A, preimplantation genetic testing for aneuploidy.

Figure 2: Aneuploidy rates reported in human preimplantation blastocyst derived from couples receiving preimplantation genetic testing for inherited disorders. Aneuploidy rates for individual studies and weighted average (Top bar) is shown. Bars are ordered in descending order by the number of embryos analysed. MFA, mean female age.

Figure 3A: Proportion of embryos being suitable for transfer prior to (green) and post (blue) aneuploidy screening in couples receiving preimplantation genetic testing for inherited disorders. Individual studies and weighted average (Top bar) are shown sorted in descending order by the number of embryos analysed. P-values were calculated using Chi square test. PGT-A, preimplantation genetic testing for aneuploidy.

Figure 3B: The effect of aneuploidy screening on the proportion of embryos being suitable for transfer in couples receiving preimplantation genetic testing for monogenic disorders (blue) or

structural rearrangements (green). P-values were calculated using Chi square test. PGT-M: Preimplantation genetic testing for monogenic disorder; PGT-SR: Preimplantation genetic testing for structural rearrangements.

Figure 4: Clinical outcomes in the reference (blue) and PGT-A (green) groups reported by the three historical cohort studies by A) Rechitsky *et al.*,[54] B) Goldman *et al.*,[50] and C) Hou *et al.*.[34] D) The average number of embryos transferred in the reference and PGT-A groups in the four historical cohort studies. P-values marked with * were reported by the authors, while unmarked p-values were calculated for the purpose of this review using two sided Fischer's exact test. It should be noted that the p-value for differences in live birth rates reported by Goldman *et al.* was 1, which is impossible with the outcomes given. [50] Hence the correct p-value was calculated, and the corresponding author contacted to verify the correct P-value, which she reported as 0.43 in agreement with our calculation. Underlying numbers were not reported by Goldman *et al.*, which indicated by (-/-) in the figure 4B. PGT-A: Preimplantation genetic testing for aneuploidy.

Table 1: Overview of the articles fulfilling criteria for inclusion.

Reference	Indication	Patients with blatocyst biopsy	Mean female age	Blastocysts succesfully analyzed	PGT-A platform	Aneuploidy rate (%)	Clinical outcomes	Reference group included
Alfarawati *et al.*, 2011[45]	PGT-SR	8	NA	56	CGH + aCGH	44.6	No	No
Treff *et al.*, 2011[18]	PGT-SR	18/15	NA/31.2	122	SNP array	33.6	Yes[a,b,c,e,f]	No
Colls *et al.*, 2012[48]	PGT-SR	10	33.4	75	aCGH	53.3	No	No
Tan *et al.*, 2013[38]	PGT-SR	169	30.2	717	SNP array	26.2	Yes[b,c,d,f]	No
Treff *et al.*, 2013[53]	PGT-M	6	NA	21	NGS	19.0	No	No
Yin *et al.*, 2013[55]	PGT-SR	14	NA	29	NGS	17.2	No	No
Tan *et al.*, 2014[32]	PGT-SR	297	30.9	1217	NGS or SNP array	27.0	Yes[b,c,d,e,f]	No
Tobler *et al.*, 2014[35]	PGT-SR	NA	NA	172	SNP array or aCGH	21.5	Yes[3]	No
Bono *et al.*, 2015[39]	PGT-SR	28	NA	102	NGS	51.0	No	No
Fan *et al.*, 2015[43]	PGT-SR	3	NA	18	NGS	33.3	No	No
Idowu *et al.*, 2015[49]	PGT-SR	NA	33.7	102	SNP array	24.0	Yes[a,c,f]	No
Rechitsky *et al.*, 2015[54]	PGT-M	NA	NA	1498	SNP array	33.6	Yes[d,f,g]	Yes
Goldman *et al.*, 2016[50]	PGT-M	47	32.4	313	aCGH	56.5	Yes[b,d,f]	Yes
Zhang *et al.*, 2016[51]	PGT-SR	16	31.9	74	NGS	29.7	No	No
Zimmerman *et al.*, 2016[56]	PGT-M	43	33.4	300	qPCR	28.3	Yes[a,b,c,f]	No
Ben-Nagi *et al.*, 2017[47]	PGT-M/PGT-SR	67	NA	422	Karyomapping	30.3	Yes[b,d,e]	No
Christodoulou *et al.*, 2017[41]	PGT-SR	34	32.5	195	aCGH	37.4	Yes[a,b,d,e,f]	No
Minasi *et al.*, 2017[36]	PGT-M/PGT-SR	227	35.4/38.1	1067	aCGH	50.6	Yes[a,c,e,f]	No
Xu *et al.*, 2017[44]	PGT-SR	16	NA	108	NGS	22.4	Yes[f]	No
Zhang *et al.*, 2017[52]	PGT-SR	11	29.2	68	SNP array	29.4	Yes[f] *	No
Del Rey *et al.*, 2018[42]	PGT-M	9	NA	12	NGS	83.3	No	No
Li *et al.*, 2018[46]	PGT-M	36	31.9	175	Karyomapping	22.9	Yes[c]	No
Volozonoka *et al.*, 2018[40]	PGT-M	9	35.3	32	aCGH	37.5	Yes[g] **	No
Wang *et al.*, 2018[33]	PGT-SR	11	30.6	103	SNP array	24.3	Yes[g] **	No
Xie *et al.*, 2018[37]	PGT-SR	NA	NA	606	SNP array	29.2	No	No

Hou *et al.*, 2019[34]	PGT-M	98	30.9	646	Karyomapping or NGS	33.6	Yes[b,d,e,f]	Yes

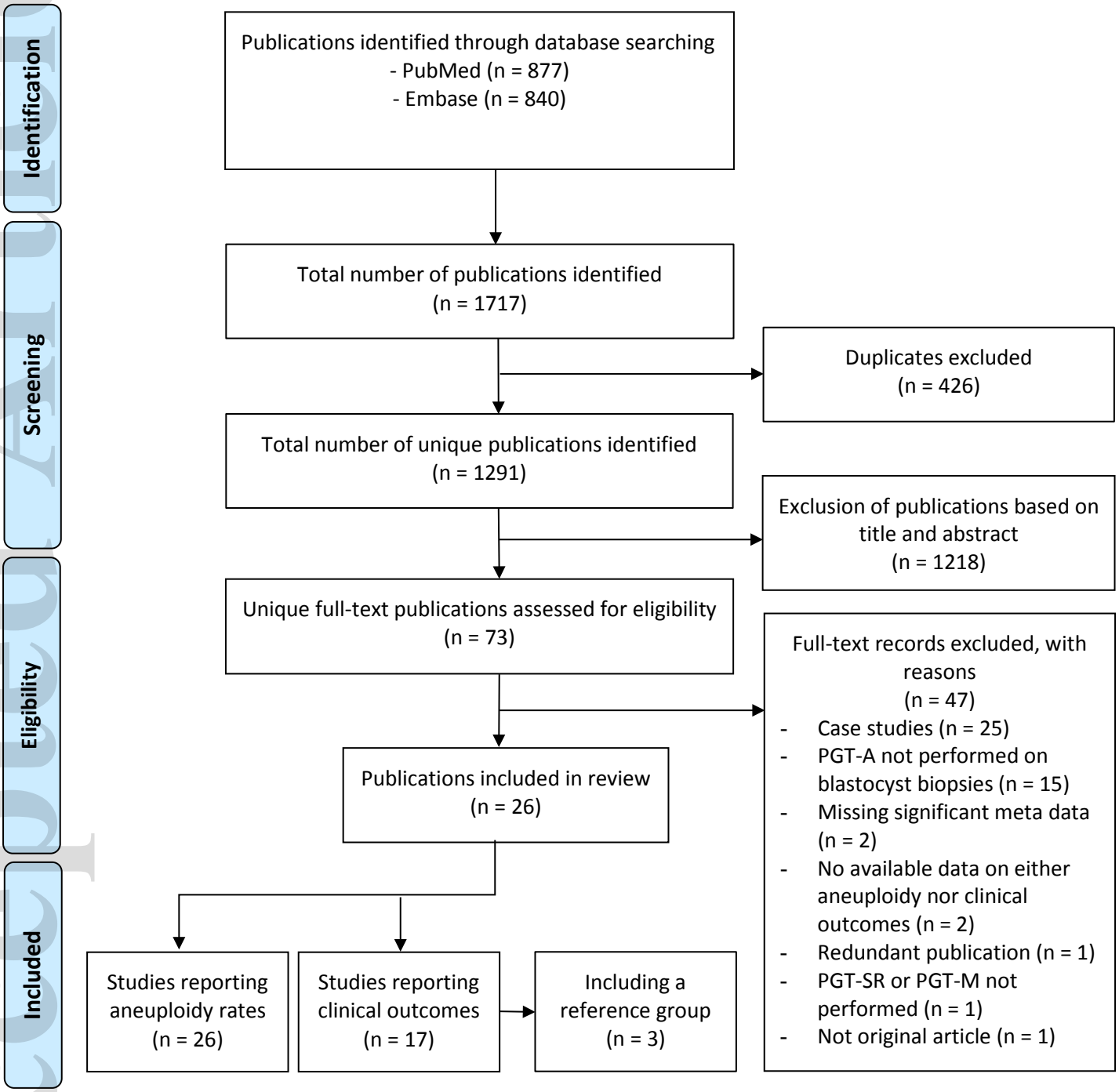
Clinical outcomes reported: *[a]Positive hCG; [b]Gestational sacs/implantation rate; [c]Fetal heartbeat/clinical pregnancy; [d]Miscarriage/spontaneous abortion; [e]Ongoing pregnancy, [f]Live birth/delivery rate, [g]Pregnancy (Not defined)*

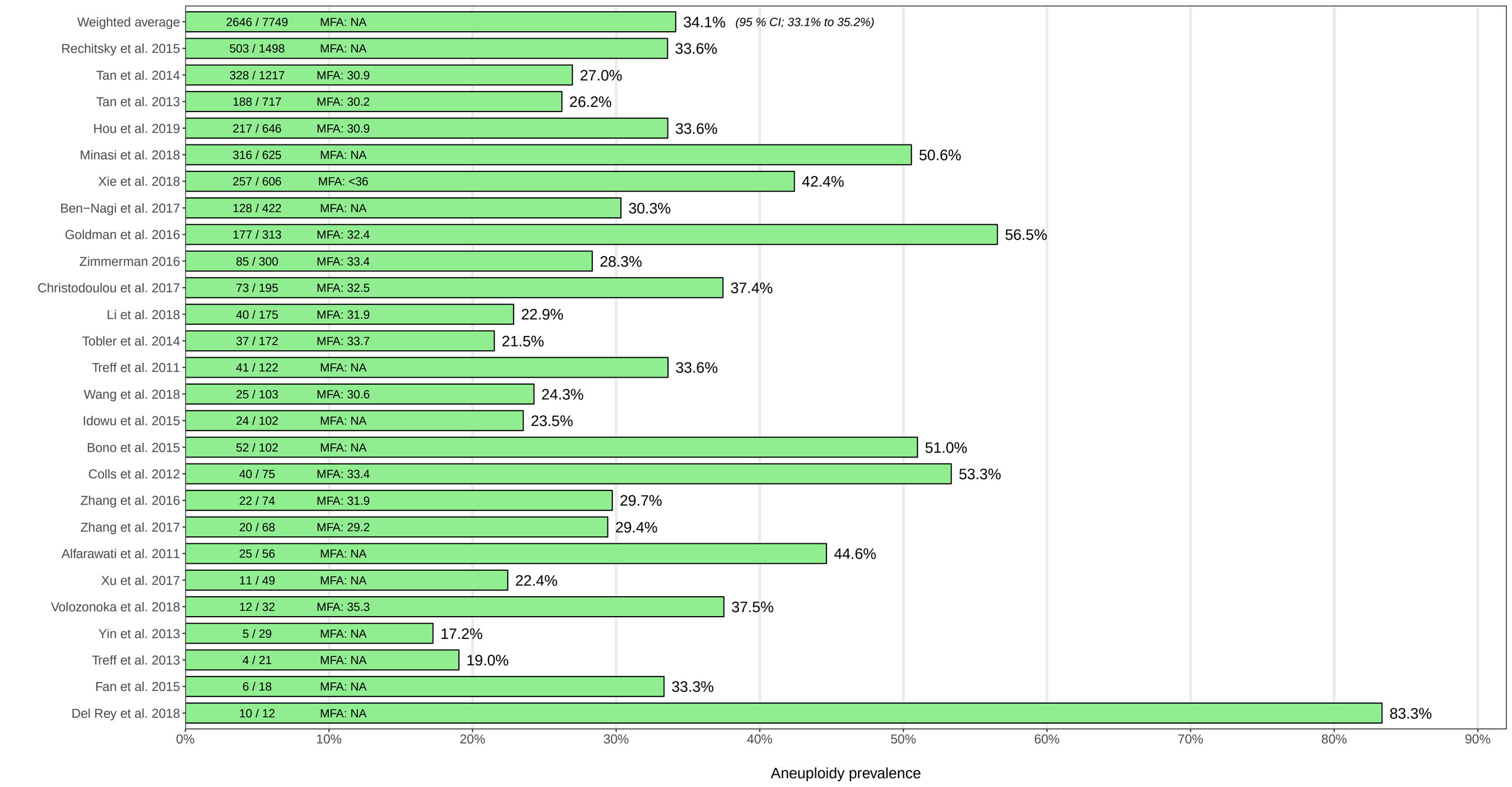
**Report on outcomes from embryo transfer in one patient*

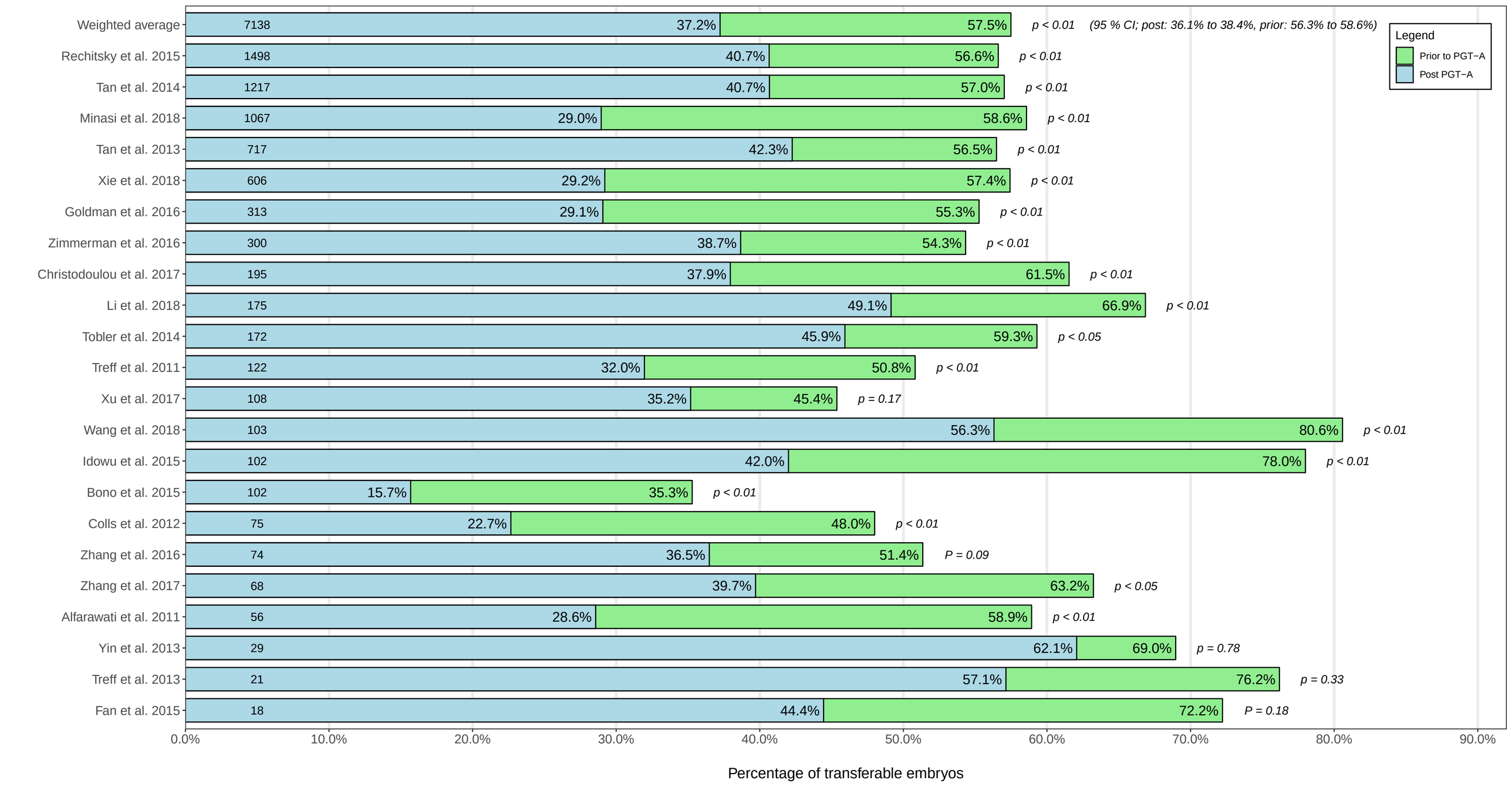
***Report on outcomes from embryo transfers in two patients*

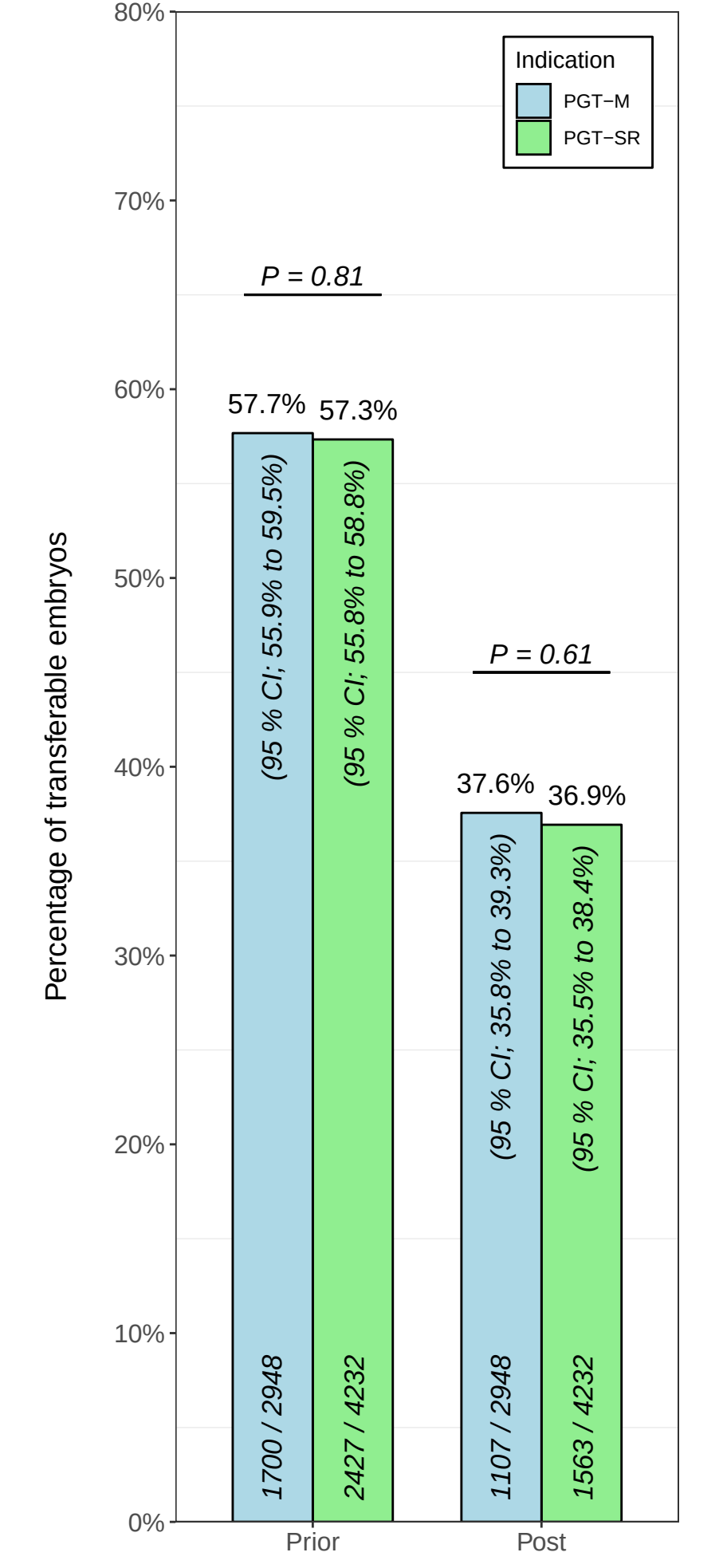
Abbreviations: *aCGH: Array comparative genomic hybridization; CGH: Comparative genomic hybridization; hCG: Human chorionic gonadotropin; NA: Not available; NGS: Next generation sequencing; PGT-A: Preimplantation genetic testing for aneuploidy; PGT-M: Preimplantation genetic testing for monogenic disorders; PGT-SR: Preimplantation genetic testing for structural*

Screening flow diagram



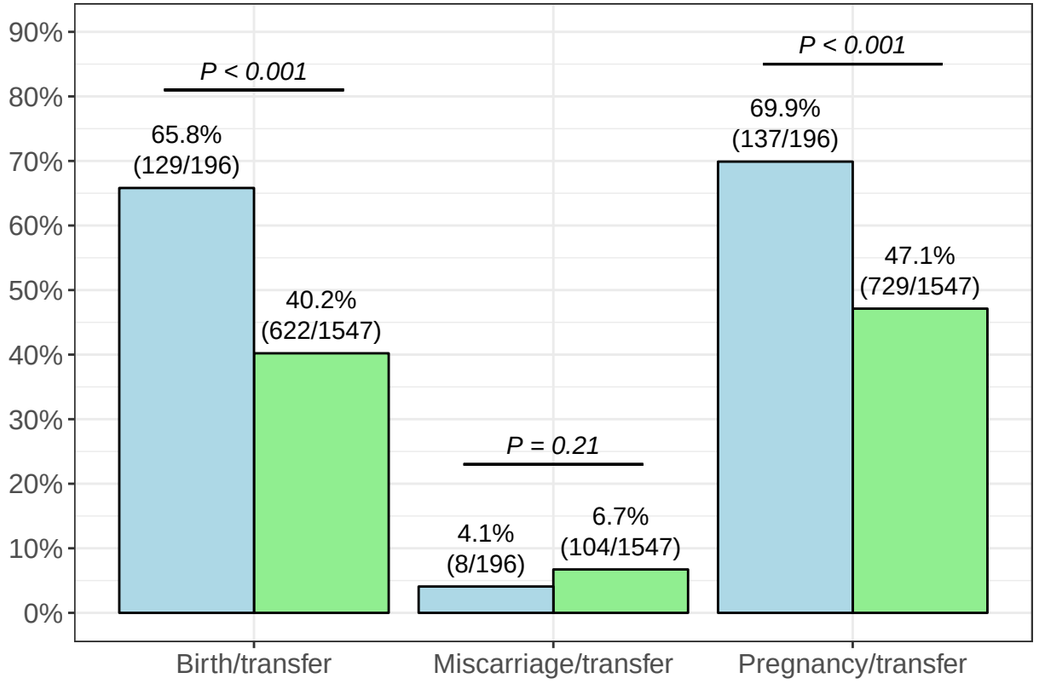

Weighted average
2646 / 7749
MFA: NA
34.1%
(95 % CI; 33.1% to 35.2%)
Rechitsky et al. 2015
503 / 1498
MFA: NA
33.6%
Tan et al. 2014
328 / 1217
MFA: 30.9
27.0%
Tan et al. 2013
188 / 717
MFA: 30.2
26.2%
Hou et al. 2019
217 / 646
MFA: 30.9
33.6%
Minasi et al. 2018
316 / 625
MFA: NA
50.6%
Xie et al. 2018
257 / 606
MFA: <36
42.4%
Ben−Nagi et al. 2017
128 / 422
MFA: NA
30.3%
Goldman et al. 2016
177 / 313
MFA: 32.4
56.5%
Zimmerman 2016
85 / 300
MFA: 33.4
28.3%
Christodoulou et al. 2017
73 / 195
MFA: 32.5
37.4%
Li et al. 2018
40 / 175
MFA: 31.9
22.9%
Tobler et al. 2014
37 / 172
MFA: 33.7
21.5%
Treff et al. 2011
41 / 122
MFA: NA
33.6%
Wang et al. 2018
25 / 103
MFA: 30.6
24.3%
Idowu et al. 2015
24 / 102
MFA: NA
23.5%
Bono et al. 2015
52 / 102
MFA: NA
51.0%
Colls et al. 2012
40 / 75
MFA: 33.4
53.3%
Zhang et al. 2016
22 / 74
MFA: 31.9
29.7%
Zhang et al. 2017
20 / 68
MFA: 29.2
29.4%
Alfarawati et al. 2011
25 / 56
MFA: NA
44.6%
Xu et al. 2017
11 / 49
MFA: NA
22.4%
Volozonoka et al. 2018
12 / 32
MFA: 35.3
37.5%
Yin et al. 2013
5 / 29
MFA: NA
17.2%
Treff et al. 2013
4 / 21
MFA: NA
19.0%
Fan et al. 2015
6 / 18
MFA: NA
33.3%
Del Rey et al. 2018
10 / 12
MFA: NA
83.3%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Aneuploidy prevalence


Weighted average
Rechitsky et al. 2015
Tan et al. 2014
Minasi et al. 2018
Tan et al. 2013
Xie et al. 2018
Goldman et al. 2016
Zimmerman et al. 2016
Christodoulou et al. 2017
Li et al. 2018
Tobler et al. 2014
Treff et al. 2011
Xu et al. 2017
Wang et al. 2018
Idowu et al. 2015
Bono et al. 2015
Colls et al. 2012
Zhang et al. 2016
Zhang et al. 2017
Alfarawati et al. 2011
Yin et al. 2013
Treff et al. 2013
Fan et al. 2015
7138
1498
1217
1067
717
606
313
300
195
175
172
122
108
103
102
102
75
74
68
56
29
21
18
37.2%
40.7%
40.7%
29.0%
42.3%
29.2%
29.1%
38.7%
37.9%
49.1%
45.9%
32.0%
35.2%
56.3%
42.0%
15.7%
22.7%
36.5%
39.7%
28.6%
62.1%
57.1%
44.4%
57.5%
56.6%
57.0%
58.6%
56.5%
57.4%
55.3%
54.3%
61.5%
66.9%
59.3%
50.8%
45.4%
80.6%
78.0%
35.3%
48.0%
51.4%
63.2%
58.9%
69.0%
76.2%
72.2%
p < 0.01 (95 % CI; post: 36.1% to 38.4%, prior: 56.3% to 58.6%)
p < 0.01
p < 0.01
p < 0.01
p < 0.01
p < 0.01
p < 0.01
p < 0.01
p < 0.01
p < 0.01
p < 0.05
p < 0.01
p = 0.17
p < 0.01
p < 0.01
p < 0.01
p < 0.01
P = 0.09
p < 0.05
p < 0.01
p = 0.78
p = 0.33
P = 0.18
Legend
Prior to PGT−A
Post PGT−A
0.0%
10.0%
20.0%
30.0%
40.0%
50.0%
60.0%
70.0%
80.0%
90.0%
Percentage of transferable embryos


Indication
PGT−M
PGT−SR
Percentage of transferable embryos
80%
70%
60%
50%
40%
30%
20%
10%
0%
P = 0.81
P = 0.61
57.7%
57.3%
37.6%
36.9%
(95 % CI; 55.9% to 59.5%)
(95 % CI; 55.8% to 58.8%)
(95 % CI; 35.8% to 39.3%)
(95 % CI; 35.5% to 38.4%)
1700 / 2948
2427 / 4232
1107 / 2948
1563 / 4232
Prior
Post

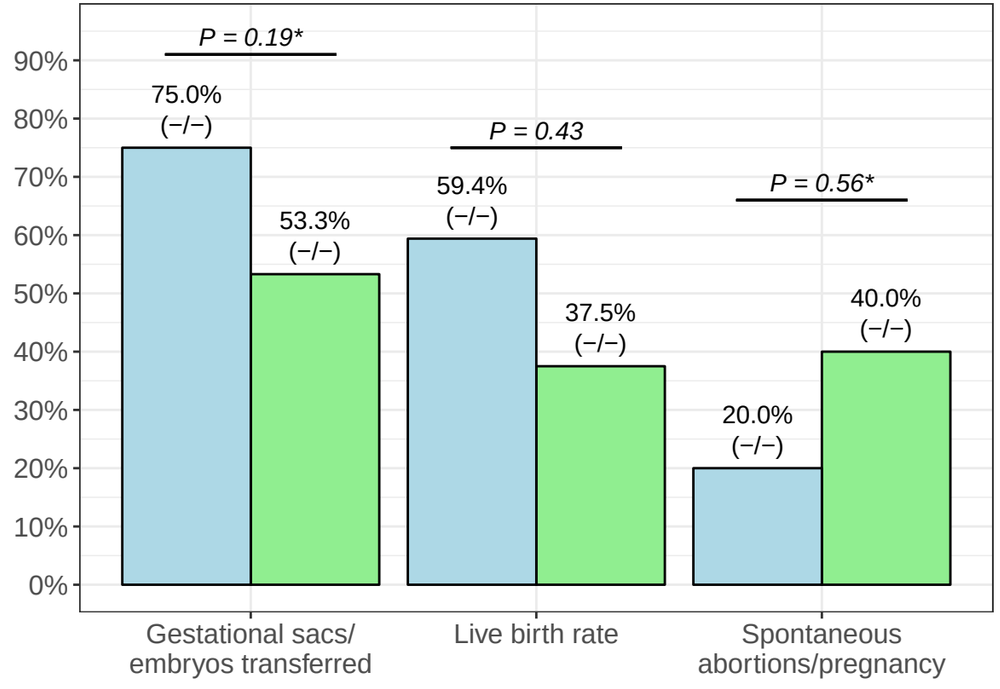
A)

Clinical outcomes reported by Rechitsky et al. 2015



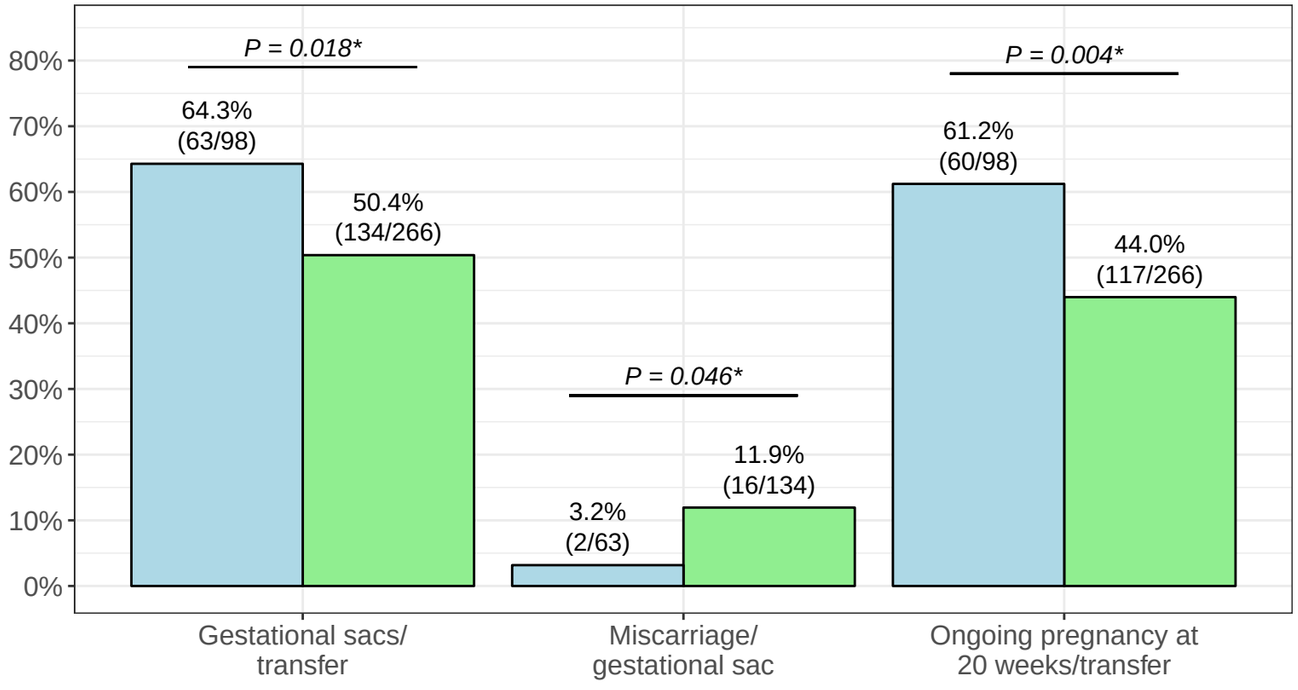
B)

Clinical outcomes reported by Goldman et al. 2016



C)

Clinical outcomes reported by Hou et al. 2019



D)

Average number of embryos transferred